ESH Position Paper: Renal denervation – an interventional therapy of resistant hypertension

Roland E. Schmieder[a], Josep Redon[b], Guido Grassi[c,k], Sverre E. Kjeldsen[d], Giuseppe Mancia[e], Krzysztof Narkiewicz[f], Gianfranco Parati[g], Luis Ruilope[h], Philippe van de Borne[i], and Costas Tsioufis[j]

Experts from the European Society of Hypertension prepared this position paper in order to summarize current evidence, unmet needs and practical recommendations on the application of percutaneous transluminal ablation of renal nerves [renal denervation (RDN)] as a novel therapeutic strategy for the treatment of resistant hypertension. The sympathetic nervous activation to the kidney and the sensory afferent signals to the central nervous system represent the targets of RND. Clinical studies have documented that catheter-based RDN decreases both efferent sympathetic and afferent sensory nerve traffic leading to clinically meaningful systolic and diastolic blood pressure (BP) reductions in patients with resistant hypertension. This position statement intends to facilitate a better understanding of the effectiveness, safety, limitations and issues still to be addressed with RDN.

Keywords: European Society of Hypertension, interventional therapy, resistant hypertension

Abbreviations: BP, blood pressure; RDN, renal denervation

THE GLOBAL BURDEN OF UNCONTROLLED HYPERTENSION

Arterial hypertension affects nowadays approximately 25% of the global adult population and its prevalence and consequent health cost is predicted to rise to 1.5 billion hypertensive patients in 2025 [1]. There is a linear relationship between blood pressure (BP) values and cardiovascular risk [2,3] and according to a worldwide analysis 7.6 million premature deaths (about of 13.5% of total deaths), 54% of strokes and 47% of events due to ischemic heart disease are attributed to high BP [4]. Most importantly even modest BP reduction is accompanied by significant attenuation of the overall cardiovascular morbidity and mortality, irrespective of the starting BP level [5–8]. Despite appropriate antihypertensive treatment BP goals are not achieved in a large proportion of patients, the so-called resistant hypertensive patients.

According to the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) and Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) guidelines, resistant hypertension is defined as persistence of BP levels above goal in spite of the concurrent use of three antihypertensive agents in adequate doses from different classes including a diuretic [5,6]. The exact prevalence of resistant hypertension is difficult to determine but depending on the population and the hypertension center considered it ranges from 5 to 30%, [9–12]. Failure to reach BP goals despite therapeutic interventions accelerates target organ damage and sets patients at high risk for major cardiovascular events [5,6,13].

Along these lines, developing additional approaches to the current management of resistant hypertension consisting of lifestyle modification combined with poly-pharmacotherapy is a clinical priority. Percutaneous catheter-based transluminal renal ablation [from now on referred to as renal denervation (RDN)] by delivery of radiofrequency energy is emerging as a new approach to achieve sustained BP reduction in patients with resistant hypertension [14–17]. Within the past year, the innovative method of RDN has progressively entered clinical practice in many countries, for the treatment of resistant hypertensive patients. The potential for its clinical use is based on the role of sympathetic overactivity in the maintenance of high BP values.

Journal of Hypertension 2012, 30:837–841

[a]University Hospital Erlangen, Nephrology and Hypertension, Erlangen, Germany, [b]University of Valencia, Internal Medicine, Hypertension Unit, Valencia, Spain, [c]Clinica Medica, Ospedale S. Gerardo dei Tintori, Monza (Milan), Italy, [d]University of Oslo, Department of Cardiology at Ullevaal Hospital, Oslo, Norway, [e]University of Milano-Bicocca, Department of Medicine, S. Gerardo Hospital, Monza, Italy, [f]Medical University of Gdansk, Department of Hypertension and Diabetology, Gdansk, Poland, [g]Department of Cardiology, S.Luca Hospital, Istituto Auxologico Italiano & Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Milan, Italy, [h]University Autonoma & Hypertension Unit, Hospital 12 de Octubre, Madrid, Spain, [i]Department of Cardiology, Erasme Hospital, Brussels, Belgium, [j]University of Athens, First Cardiology Clinic, Hippokration Hospital, Athens, Greece and [k]Istituto di Ricerche a Carattere Ccientifico IRCCS Multimedica, Sesto san Giovanni (Milan), Italy

Correspondence to Roland E. Schmieder, University Hospital Erlangen, Nephrology and Hypertension, Ulmenweg 18, 91054 Erlangen, Germany. Tel: +49 9131 8536245; fax: +49 9131 8536215; e-mail: roland.schmieder@uk-erlangen.de

Received 1 February 2012 **Revised** 21 February 2012 **Accepted** 21 February 2012

J Hypertens 30:837–841

DOI:10.1097/HJH.0b013e328352ce78

OVERALL AND RENAL SYMPATHETIC OVERACTIVITY IN HYPERTENSION

Increased sympathetic activity has been shown to characterize all hypertensive phenotypes including essential hypertension [18–20], white-coat and masked hypertension [18,21], associated with either dipping, extreme dipping, nondipping, or reverse dipping conditions [22]. This is also the case for pregnancy-induced hypertension [23], some secondary types of hypertension [24] and resistant hypertension [25]. Most notably, sympathetic nervous system overactivity involves the kidney [26] and increases progressively and in parallel with hypertension severity stages [25,27,28].

The sympathetic innervation of the kidneys is achieved through a dense network of postganglionic neurons that innervate the kidney [29,30]. The axons of preganglionic neurons exit the thoracic and lumbar sympathetic trunk and reach the pre and paravertebral sympathetic ganglia. Renal postganglionic nerves run alongside the renal artery and enter the hilus of the kidney. Thereafter, they divide into smaller nerve bundles following the blood vessels and penetrate the cortical and juxtamedullary areas. Renal sympathetic nerve activation enhances noradrenaline production and release from nerve endings, leading to renal vasoconstriction, enhanced renin secretion, increased sodium and fluid reabsorption, renal vasoconstriction, and decrease in renal blood flow and glomerular filtration rate [31].

The cell bodies of renal afferent nerves are located in the ipsilateral dorsal root ganglia (T6-L4). From there, ascending signals travel to the cardiovascular centers in the central nervous system. Renal afferent sensory nerves respond to stretch (mechanoreceptors), renal ischemia, hypoxia or other injury (chemoreceptors) by increasing renal afferent activity [32–34]. Electrical stimulation of afferent renal nerves increases BP [35] and induces mesenteric and muscle vasoconstriction [35]. Conversely, afferent renal denervation attenuates these effects and delays or prevents hypertension in several animal models [36]. Overall afferent and efferent fibers deliver an important contribution to regulation of systemic vascular resistance and BP control [37].

RENAL DENERVATION IN RESISTANT HYPERTENSION

In the past century, surgical splanchnicectomy that led to renal denervation among others improved survival of hypertensive patients when compared to conservative management available at that time [38], but the interest in this invasive surgical technique faded quite suddenly with the dawn of effective antihypertensive drug therapy.

Renal denervation is a percutaneous procedure, minimally invasive, characterized by short recovery times, and absence of significant systematic side effects. Evidence on the clinical effectiveness of this procedure in hypertensive patients comes from the Symplicity Clinical Trial Program consisting of a group of studies focusing on the effects of RDN in the treatment of resistant hypertension. These trials include the Symplicity Hypertension (HTN)-1 (with extended follow-up) and the Symplicity HTN-2 study, both already published [15–17].

Symplicity HTN-1 study and extended follow-up

Efficacy

This first-in-man proof-of-concept and safety study included 50 patients (mean age 58 ± 9 years) with severe resistant hypertension (office SBP $\geq$160 mmHg with at least three or more antihypertensive medications, including a diuretic). Baseline office SBP/DBP values were 177/101 mmHg with 5.1 antihypertensive drugs on average. RDN was achieved using a radiofrequency ablation catheter inserted through the femoral artery (Symplicity, Ardian Inc., Palo Alto, California, USA). Office SBP/DBP values after bilateral RDN were reduced by $-14/-10$, $-21/-10$, $-22/-11$, $-24/-11$, and $-27/-17$ mmHg at 1, 3, 6, 9, and 12 months, respectively. In nine patients medication was increased and in four patients decreased. After censoring data a similar effect in office SBP/DBP was observed. In a small subset of patients renal noradrenaline spillover was found to be reduced by 47% thereby demonstrating the effectiveness of sympathetic renal fibers ablation. Over a longer-term follow-up of 153 patients, including 45 patients treated with RDN in the frame of Symplicity HTN-1 Study and a larger group of similar patients treated with catheter-based RDN in a nonrandomized manner (mean age 57 years, mean office SBP/DBP 176/98 mm Hg in spite of an average of 5.1 antihypertension drugs), office SBP/DBP values were significantly reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mmHg at 1, 3, 6, 12, 18, and 24 months, respectively. These findings suggest that reduction of BP is sustained at least up to 2 years after the procedure.

Safety

The long-term safety of catheter-based RND was investigated in the extended Symplicity HTN-1 cohort ($n = 153$) in which 97% of patients (149 of 153) had no complications. The four acute procedural complications included three groin pseudoaneurysms and one renal artery dissection, all managed without further sequelae. In one patient, computed tomography (CT) angiography performed 6 months after the procedure revealed progression of an existing stenosis at the ostium of one renal artery that was successfully treated with stenting. However, the site of the stenosis was not in the area of energy delivery during RDN. Focusing on renal function, during the first year of follow-up, estimated glomerular filtration rate remained stable, and after the 2 years there were no cases of doubling of serum creatinine or of chronic kidney disease stage 4 or 5 development.

Symplicity HTN-2

Efficacy

This multicenter, prospective, randomized clinical trial included patients with resistant hypertension and office SBP at least 160 mmHg (or $\geq$150 mmHg for patients with

type 2 diabetes) [17]. Participants were randomly assigned to RDN immediately or after 6 months, without any change in the previous antihypertensive medication regimen. The primary endpoint was change in SBP at 6 months. Out of 190 patients screened for eligibility, 106 were randomized either to immediate RDN ($n=52$) or to a delayed performance of the procedure (control group) ($n=54$). Both groups had similar baseline characteristics and antihypertensive drug regimen, with the exception of estimated glomerular filtration rate. Office SBP/DBP values in the RDN group decreased by 32/12 mmHg (baseline 178/96 mmHg, $P<0.0001$), whereas no changes in the control group occurred. Differences in office SBP/DBP between the two groups at 6 months were 33/11 mmHg (control vs. RDN group; $P<0.0001$). When censored for increases in medications, these differences were 31/11 mmHg ($P<0.0001$). Ambulatory BP monitoring over 24 h was performed in a limited number ($n=20$) of patients from both groups, showing a similar albeit less pronounced pattern of BP changes 6 months after RDN (−11/−7 mmHg, $=0.006$ for SBP change, $P=0.014$ for DBP change), compared to −3/−1 mmHg in the control group. Differences in home SBP/DBP were 22/12 mmHg (control vs. RDN; $P<0.0001$). RDN resulted in satisfactory BP control in 39% or in 82% of patients, when BP control was defined as SBP less than 140 mmHg or less than 160 mmHg, respectively, the corresponding figures for the control group being 3 and 24%, respectively. Ten out of 49 patients (20%) who underwent renal denervation had drug reductions prior to the 6 months follow-up but only three out of 51 controls (6%, $P=0.04$). In a subanalysis that censored all data after drug increase BP reduction was 31/12 mmHg ($P<0.0001$) in patients who underwent renal denervation.

Safety

In Symplicity HTN-2, periprocedural events requiring treatment were rare and consisted of one femoral artery pseudoaneurysm, one postprocedural drop in BP requiring a reduction in antihypertensive drugs, one urinary tract infection, one extended hospital admission for assessment of paraesthesias, and one case of back pain that was treated with analgesics and resolved after 1 month. Seven (13%) of 52 patients who underwent renal denervation had transient intraprocedural bradycardia, some of them requiring atropine. Renal function, as assessed by serum creatinine, estimated glomerular filtration rate, and cystatin C levels were unchanged from baseline in both groups at 6 months. Six-month renal vascular imaging identified one patient with possible progression of an underlying atherosclerotic lesion, which required no therapy.

Interestingly, in another substudy of Symplicity-HTN-2 including 37 resistant hypertensive patients, RDN resulted in maximum exercise SBP/DBP drop of 21/5 mmHg and of 29/9 mmHg in the recovery period, whereas heart rate response and exercise oxygen uptake were well preserved [39].

LIMITATION AND OPEN QUESTIONS

Until the beginning of 2012 only a small number of patients have been exposed to RDN, and the follow-up is rather short. Thus, several issues needs to be further elucidated.

Regarding efficacy, there was no sham control group in the available trials, which is now part of Symplicity HTN-3 currently conducted in the US as well as in the Duration of Renal Sympathetic Activation and Hypertension study starting in Europe and Canada. Ambulatory blood pressure monitoring was available in a small (selected) portion of patients only and the observed degree of reduction was smaller compared to office and home BP [15,17]. Thus, the true antihypertensive effect of RDN, and particularly that on the prognostically important out of office BP, still needs to be determined. The long-term duration of the antihypertensive effect after RDN needs to be investigated since renal nerve fibers may regenerate [40,41]. It has to be emphasized that in the extended Symplicity HTN-1 trial there was no attenuation of the BP decrease throughout the follow-up period of 24 months suggesting that functional reinnervation did not take place over the time window considered [16]. Up to now, patients with dual renal arteries and accessory arteries have been excluded and there are no systematic data on unilateral RDN effects [15,17].

The lack of any preprocedural marker that might identify good responders to RDN (except the baseline BP) is another matter to be addressed. Despite the methodological achievements in the assessment of adrenergic function (as obtained by performing microneurography and organ specific noradrenaline spillover), no clinically applicable technique is available to indicate successful renal sympathetic fibers ablation during the procedure. So far RDN is performed in patients with severe resistant hypertension and its effect in less severe forms of hypertension is unknown. Likewise it is also unknown whether cardiovascular endpoints are prevented and mortality reduced.

Nowadays there are further experimental studies with promising results on renal sympathetic denervation performed with different techniques, using local delivery of neurotoxic drugs, cryoablation, ultrasound-induced denervation, and there are ongoing clinical trials with radiofrequency catheter using other catheter types [e.g. trials with a basket-type ablation catheter (Ablation Induced Renal Sympathetic Denervation Trial study)] [42].

The above unmet needs are summarized in Box 1.

ELIGIBILITY CRITERIA FOR RENAL DENERVATION

Based on current evidence from available clinical studies hypertensive patients are eligible for RDN if they have (severe) treatment-resistant hypertension defined by office SBP at least 160 systolic (≥150 mmHg in type 2 diabetes)

Box 1 Unmet needs in RDN

- Randomized blinded studies
- Use of 24-h ABPM to enroll patients and to assess BP reduction
- Comparison of RDN efficacy and safety when using different procedures
- Long-term maintenance of efficacy and safety
- Impact in morbidity and mortality reduction
- Cost-benefit balance studies
- Standardized certification of RDN centers

despite treatment with at least three antihypertensive drugs of different types in adequate doses, including one diuretic, which is equivalent to stage 2 or 3 hypertension [15–17].

Patients should have been evaluated by a hypertension specialist in very experienced hospital centers (e.g. ESH excellence centers). Patients should undergo a through clinical examination to confirm treatment resistance and exclude pseudoresistance as the initial steps. Attention is needed regarding nonadherence to drug therapy that is often present and not acknowledged if not rigorously investigated [6]. Persisting high office BP in spite of drug treatment should be confirmed with home and most importantly with 24-h ambulatory blood pressure monitoring, since up to one-third of treatment-'resistant' hypertensive patients have normal BP outside the office (false resistant hypertension due to persisting white-coat effect during treatment) [43]. After confirming a 'true' resistant hypertension, careful attempts should be made to identify and reverse contributing lifestyle factors, to discontinue or minimize use of BP rising substances along with an additional screening for secondary causes of hypertension, to identify those conditions when BP control could be easier with removal of the responsible factors [5,6]. Controversy exists whether use of aldosterone antagonists is a prerequisite for eligibility. SBP reduction up to 25 mmHg systolic has been reported but not all patients have such a response. In the first double-blind randomized trial, the fall in BP with spironolactone was rather modest and long-term safety is a matter of concern [44]. If hypertension is not controlled then the patient is considered a candidate for RDN.

If not already done, it is recommended to obtain renal artery imaging [e.g. CT or magnetic resonance (MR) angiography] to assess accurately renal artery anatomy before performing RDN.

It has to be emphasized that patients with treatment-resistant hypertension have almost invariably been exposed to a variety of antihypertensive medications. A large proportion of them claims intolerance to some antihypertensive drugs, and such an intolerance may be related to the typical side effects attributable to a given compound but it may also be related to a patient's psychiatric problem or unsuccessful physician/patient relationship. This represents a challenge for the hypertension specialist whose task is to diagnose true drug intolerance (e.g. by re-exposition of the intolerant drug), because only in this case a procedure of RDN may be justified.

The following exclusion criteria should also be implemented in order to safely proceed to RDN: [15–17] previous renal artery intervention (balloon angioplasty or stenting), evidence of renal artery atherosclerosis (defined as a renal artery stenosis >50%), presence of multiple main renal arteries in either kidneys or main renal arteries of less than 4 mm in diameter or less than 20 mm in length and estimated glomerular filtration rate <45 ml/min per 1.73 m^2. Patients should be in stable clinical conditions (RDN is not an emergency treatment), thus ruling out patients with recent myocardial infarction, unstable angina pectoris, or a cerebrovascular accident within the past 3–6 months.

If the patient fulfills all the eligibility criteria for RDN the procedure is consequently scheduled. The intervention should be performed by interventional cardiologists or radiologists who have been trained with this specific intervention and who are qualified to manage potential complications, such as dissection of renal artery.

Practical recommendations for RND in clinical practice are shown in Box 2.

Box 2 Today recommendations

- First step: Exclude
  - False resistant hypertension (peudoresistance) by using 24 h ambulatory blood pressure monitoring (ABPM) and home BP monitoring.
  - Secondary arterial hypertension
  - Causes which maintain high BP values and might be removed (obstructive sleep-apnea, high salt intake, BP raising drugs, severe obesity)
- Second step: Optimize antihypertensive treatment with at least three (or better four) tolerated drugs including a diuretic and an antialdosterone drug (if clinically possible, e.g. after re-evaluating renal function and the potential risk of hyperkaliemia) and check for effective BP control using ABPM before giving indication for RND
- Third step: Consider anatomic contraindications due to unresolvesd safety issues (avoid RDN in case of multiple renal arteries, main renal artery diameter of less than 4 mm or main renal artery length less than 20 mm, significant renal artery stenosis, previous angioplasty or stenting of renal artery). Likewise, eGFR should be > 45 ml/min/1.73m^2
- Overall:
  - Perform the procedure in very experienced hospital centers, such as hypertension excellence centers
  - Use devices which have demonstrate efficacy and safety in clinical studies

PERSPECTIVE

Renal denervation may have beneficial effects in other conditions characterized by excessive sympathetic activation, and is currently under assessment in several clinical investigations. Until these results are available we should use RDN in patients with treatment-resistant hypertension only fulfilling the above reported criteria after careful selection in hypertension excellence centers. RDN should be performed in very experienced hypertension excellence centers by well trained interventionalists throughout Europe.

ACKNOWLEDGEMENTS

Conflicts of interest

RES has received travel support, consulting and speaker fees from Medtronic. RES's institution (University Hospital Erlangen, Germany) has received research grants from Medtronic. No other authors have conflicts of interest to declare.

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; 365:217–223.
2. Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, *et al.* Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008; 336:1121–1123.
3. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360:1903–1913.
4. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008; 371:1513–1518.

5. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, *et al*. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009; 27:2121–2158.
6. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al*. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25:1105–1187.
7. Zhang Y, Zhang X, Liu L, Zanchetti A. Is a systolic blood pressure target <140 mmHg indicated in all hypertensives? Subgroup analyses of findings from the randomized FEVER trial. *Eur Heart J* 2011; 32: 1500–1508.
8. Czernichow S, Zanchetti A, Turnbull F, Barzi F, Ninomiya T, Kengne AP, *et al*. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. *J Hypertens* 2011; 29:4–16.
9. Prugger C, Keil U, Wellmann J, de Bacquer D, de Backer G, Ambrosio GB, *et al*. Blood pressure control and knowledge of target blood pressure in coronary patients across Europe: results from the EUROASPIRE III survey. *J Hypertens* 2011; 29:1641–1648.
10. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, *et al*. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension* 2008; 51:1403–1419.
11. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, *et al*. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension* 2011; 57:898–902.
12. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. *Circulation* 2011; 124:1046–1058.
13. Cuspidi C, Macca G, Sampieri L, Michev I, Salerno M, Fusi V, *et al*. High prevalence of cardiac and extracardiac target organ damage in refractory hypertension. *J Hypertens* 2001; 19:2063–2070.
14. Schlaich MP, Sobotka PA, Krum H, Whitbourn R, Walton A, Esler MD. Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept. *Hypertension* 2009; 54:1195–1201.
15. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, *et al*. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; 373:1275–1281.
16. Simplicity HTN-1 Investigators 2011. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011; 57:911–917.
17. Simplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; 376:1903–1909.
18. Grassi G. Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives. *Hypertension* 2009; 54:690–697.
19. Grassi G, Seravalle G, Bertinieri G, Turri C, Dell'Oro R, Stella ML, *et al*. Sympathetic and reflex alterations in systo-diastolic and systolic hypertension of the elderly. *J Hypertens* 2000; 18:587–593.
20. Flaa A, Eide IK, Kjeldsen SE, Rostrup M. Sympathoadrenal stress reactivity is a predictor of future blood pressure: an 18-year follow-up study. *Hypertension* 2008; 52:336–341.
21. Grassi G, Seravalle G, Trevano FQ, Dell'oro R, Bolla G, Cuspidi C, *et al*. Neurogenic abnormalities in masked hypertension. *Hypertension* 2007; 50:537–542.
22. Grassi G, Seravalle G, Quarti-Trevano F, Dell'Oro R, Bombelli M, Cuspidi C, *et al*. Adrenergic, metabolic, and reflex abnormalities in reverse and extreme dipper hypertensives. *Hypertension* 2008; 52:925–931.
23. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia: a state of sympathetic overactivity. *N Engl J Med* 1996; 335:1480–1485.
24. Schlaich MP, Socratous F, Hennebry S, Eikelis N, Lambert EA, Straznicky N, *et al*. Sympathetic activation in chronic renal failure. *J Am Soc Nephrol* 2009; 20:933–939.
25. Tsioufis C, Kordalis A, Flessas D, Anastasopoulos I, Tsiachris D, Papademetriou V, *et al*. Pathophysiology of resistant hypertension: the role of sympathetic nervous system. *Int J Hypertens* 2011; 2011:642416.
26. Esler M, Lambert G, Jennings G. Regional norepinephrine turnover in human hypertension. *Clin Exp Hypertens A* 1989; 11 (Suppl 1):75–89.
27. Anderson EA, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. *Hypertension* 1989; 14:177–183.
28. Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Mancia G. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. *Hypertension* 1998; 31:68–72.
29. Barajas L, Liu L, Powers K. Anatomy of the renal innervation: intrarenal aspects and ganglia of origin. *Can J Physiol Pharmacol* 1992; 70:735–749.
30. Luff SE, Hengstberger SG, McLachlan EM, Anderson WP. Distribution of sympathetic neuroeffector junctions in the juxtaglomerular region of the rabbit kidney. *J Auton Nerv Syst* 1992; 40:239–253.
31. DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. *Am J Physiol Regul Integr Comp Physiol* 2010; 298:R245–R253.
32. Ditting T, Freisinger W, Siegel K, Fiedler C, Small L, Neuhuber W, *et al*. Tonic postganglionic sympathetic inhibition induced by afferent renal nerves? *Hypertension* 2012; 59:467–476.
33. Stella A, Zanchetti A. Functional role of renal afferents. *Physiol Rev* 1991; 71:659–682.
34. Hausberg M, Kosch M, Harmelink P, Barenbrock M, Hohage H, Kisters K, *et al*. Sympathetic nerve activity in end-stage renal disease. *Circulation* 2002; 106:1974–1979.
35. Calaresu FR, Stella A, Zanchetti A. Haemodynamic responses and renin release during stimulation of afferent renal nerves in the cat. *J Physiol* 1976; 255:687–700.
36. DiBona GF, Kopp UC. Neural control of renal function. *Physiol Rev* 1997; 77:75–197.
37. Doumas M, Papademetriou V, Douma S, Faselis C, Tsioufis K, Gkaliagkousi E, *et al*. Benefits from treatment and control of patients with resistant hypertension. *Int J Hypertens* 2010; 2011:318549.
38. Smithwick RH, Thompson JE. Splanchnicectomy for essential hypertension; results in 1266 cases. *JAMA* 1953; 152:1501–1504.
39. Ukena C, Mahfoud F, Kindermann I, Barth C, Lenski M, Kindermann M, *et al*. Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol* 2011; 58:1176–1182.
40. Hansen JM, Abildgaard U, Fogh-Andersen N, Kanstrup IL, Bratholm P, Plum I, *et al*. The transplanted human kidney does not achieve functional reinnervation. *Clin Sci (Lond)* 1994; 87:13–20.
41. Gazdar AF, Dammin GJ. Neural degeneration and regeneration in human renal transplants. *N Engl J Med* 1970; 283:222–224.
42. Safety and Efficacy Study of Renal Artery Ablation in Resistant Hypertension Patients (ARSENAL). ClinicalTrialsgov.NCT01438229.
43. Banegas JR, Messerli FH, Waeber B, Rodriguez-Artalejo F, de la Sierra A, Segura J, *et al*. Discrepancies between office and ambulatory blood pressure: clinical implications. *Am J Med* 2009; 122:1136–1141.
44. Vaclavik J, Sedlak R, Plachy M, Navratil K, Plasek J, Jarkovsky J, *et al*. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. *Hypertension* 2011; 57:1069–1075.